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REMARKS

In response to the Examiner's objection to the Abstract, the Abstract has been amended so that the first sentence is complete. Please find enclosed a new copy of the declaration as requested. Claims 1-12 and 17-19 have been canceled. Claim 13 has been amended to include the additional step of identifying the potential target protein as a target protein for pharmaceutical intervention based at least in part on the repeated comparisons. Support for this amendment is found, for example, in the specification on page 10, lines 9-17. In this example, the specification discloses identifying a protein in a pathogen's metabolic pathway as the best candidate for pharmaceutical intervention if its interaction fingerprint has a lowest average and/or maximum overlap to the proteins of the human genome. Claim 16 has been amended to clarify that the claimed system is implemented on a computer. Such an amendment finds support in the original claim because those skilled in the art would recognize that a "database" and a "search and computation engine" are implemented on a computer. Furthermore, on page 1, lines 27-29, the specification demonstrates that the context of the disclosure is computer-implemented methods and systems by referring to commercially available software products.

Rejections Under § 101: Statutory Subject Matter

The Examiner rejected Claims 13-16 as being directed to non-statutory subject matter. With respect to the method Claims 13-15, the Examiner asserted that the claims are "merely a mathematical manipulation of data." Office Action, page 2. The Applicants respectfully submit that Claims 13-15 contain limitations directed to manipulation of data that represent specific physical objects and as such, are directed to patentable subject matter. See M.P.E.P. § 2106(IV)(B)(2)(b)(i) ("Manipulation of Data Representing Physical Objects or Activities").

Claim 13 requires selecting a first potential target protein. Claim 13 also requires retrieving a first interaction fingerprint corresponding to the potential target protein and a corresponding set of ligands. Furthermore, Claim 14 requires retrieving interaction fingerprints for substantially all proteins encoded by a selected genome. The proteins, ligands, and genome referred to in Claims 13-15 are specific physical objects that exist in the physical world. As such, the interaction fingerprints are derived from data that represent specific physical objects. For example, the specification indicates one method of obtaining interaction fingerprints. Three-dimensional protein structures are derived using sequences retrieved from a genomics database.

Specification, pages 5-6. Genomics databases are created by experimentally determining gene sequences in a laboratory for genes that encode expressed proteins. Once the three dimensional protein structures are derived, docking simulations between the protein and a series of ligand models provide an interaction fingerprint. Specification, pages 6-7. In another example, the three dimensional protein structures are determined using experimental measurements of the proteins such as x-ray crystallography. Specification, page 6. Thus, the interaction fingerprints are obtained from data corresponding to physically measured gene sequences or protein structures.

In Arrhythmia Research Technology, Inc. v. Corazonix Corp., 958 F.2d 1053 (Fed. Cir. 1992), the Federal Circuit held that algorithms that are applied to physical elements are patentable subject matter. The method claim at issue in Arrhythmia was a method for analyzing electrocardiograph signals. The claim contained the steps of "converting a series of QRS signals...applying a portion of said time segments...to high pass filter means; determining an arithmetic value...and comparing said value." *Id.* at 1055. Thus, the claim in Arrhythmia presents an algorithm that operates on specific data (i.e., "QRS signals") representing a specific physical object (i.e., heart function). The Court held the claim patentable, noting that the "input signals are not abstractions; they are related to the patient's heart function." 958 F.2d at 1059. Similarly, the interaction fingerprints in Claims 13-15 are not abstractions; they are related to gene sequences, protein structure, and the structure of ligands. Thus, the interaction fingerprints constitute specific data that are an intangible representation of specific physical objects, namely proteins and protein-ligand complexes. See M.P.E.P. § 2106(IV)(B)(2)(b)(i). *See also In re Abele*, 684 F.2d 902 (CCPA 1982) (allowing a method claim directed to an algorithm that used "X-ray attenuation data" because the data used by the algorithm was obtained from a specific physical process).

The court in Arrhythmia also noted that the resultant output of the claimed algorithm was not an abstract number, but rather a signal related to the patient's heart activity. 958 F.2d at 1059. In a similar manner, the process in Claims 13-15 does not produce an abstract result, but rather a result related to a physical object. Claims 13-15 result in the identification of a target protein for pharmaceutical intervention. The target protein is an existing physical entity. Therefore, the process of Claims 13-15 has "real world value" and is analogous to the process

claim in Arrhythmia. See M.P.E.P. § 2106(IV)(B)(2)(b)(i). Applicants respectfully assert that Claims 13-15 are directed to statutory subject matter for the same reasons as the claim in Arrhythmia.

The Examiner also rejected Claim 16 as being directed to non-statutory subject matter. The Examiner asserted that Claim 16 lacks a physical or hardware limitation. See Office Action, page 3. The Applicants have amended Claim 16 to clarify that the claimed system is implemented on a computer. Furthermore, the Applicants respectfully submit that one skilled in the art would recognize that Claim 16 requires hardware. Claim 16 contains the elements of a database and a search and computation engine. One skilled in the art would recognize that these elements are implemented on a hardware device, such as a computer. A database implies more than just the collection of information contained in the database. The database also includes the hardware means to store the information. Likewise, a search and computation engine implies more than just an abstract algorithm for searching and computing. Such an engine also includes the hardware means for implementing the searching and computation functions.

Because Claim 16 contains hardware limitations, it is directed to statutory subject matter. *See In re Warmerdam*, 33 F.3d 1354 (Fed. Cir. 1994). The application at issue in *In re Warmerdam* contained a claim to a "machine having a memory which contains data...generated by" a specified algorithm. *Id.* at 1358. The Court unequivocally stated that the claim "is for a machine, and is clearly patentable subject matter." *Id.* at 1360; *see also* M.P.E.P. § 2106(IV)(B)(2)(a). The system claimed in Claim 16 contains hardware elements analogous to the "memory" in *In re Warmerdam* (i.e., a "database" and a "search and computation engine"). As such, the Applicants respectfully submit that Claim 16 is directed to patentable subject matter.

The Examiner further indicated that Claim 16 does not have a practical application in the technological arts. See Office Action, page 3. The Applicants respectfully submit that a system providing a database that stores both gene sequences and interaction fingerprints of proteins in conjunction with a means to retrieve and compare the interaction fingerprints has practical application in the technological arts. Examples of such applications are provided in the specification. See Specification, pages 8-11. For example, the system of Claim 16 could be used for protein functional association, toxicity assessment, identification of targets for pharmaceutical intervention, chemical family identification for drug candidates, selectivity

identification, or protein family profiling. All of these examples provide a concrete, tangible, and useful result. The Applicants respectfully submit that Claim 16 is directed to statutory subject matter.

Rejections Under § 101: Utility

The Examiner rejected Claims 13-16 under 35 U.S.C. § 101 for lack of utility. Specifically, the Examiner noted that the usefulness of identifying a target protein is not apparent because there "is no step of identifying a protein." Office Action, page 3. Furthermore, the Examiner asserted that the specification does not state the usefulness of comparing protein fingerprints. See Office Action, pages 3-4. The Examiner is under the impression that further research, mathematical calculations, and method steps would be required to use the claimed method and system. See Office Action, page 4.

With respect to Claims 13-15, the Applicants respectfully submit that the claimed method provides "immediate benefit to the public" in a "real world" context. See *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980). Claim 13 sets forth a method of identifying a protein for pharmaceutical intervention. As amended, Claim 13 provides a series of steps that culminate in the step of identifying a potential target protein for pharmaceutical intervention. The specification provides several examples of identifying target proteins. For example, under the heading "Toxicity Assessment," a potential target protein is evaluated for the toxicity of a drug that targets it. *See* Specification, page 9. In another example, under the heading "Identification of Targets for Pharmaceutical Intervention," a target protein in the metabolic pathway of a disease pathogen is identified. *See* Specification, pages 9-10. Other examples disclosed in the specification include chemical family identification for drug candidates, selectivity identification, and protein family profiling. *See* Specification, pages 10-11.

The fact that further research would be required to develop a drug after identifying the target protein does not destroy the utility of the method. For example, it is substantially useful to drug researchers to have a drug target identified whose inactivation would result in lower side effects than the inactivation of other targets. The methods described in the specification significantly reduce drug development time because the drug researcher could focus on a single drug target. On the other hand, if a drug researcher arbitrarily chose one of multiple possible targets, the developed drug may have undesired side effects that could have been avoided if the

researcher had used the disclosed method to select an alternative protein target. Thus, the method in Claims 13-15 provides an "immediate benefit to the public."

Similarly, with respect to Claim 16 the specification discloses several utilities that are provided by the claimed system. For example, a drug researcher could use the system of Claim 16 for toxicity assessment, identification of targets for pharmaceutical intervention, chemical family identification for drug candidates, selectivity identification, and protein family profiling. Thus, a drug researcher could use the system of Claim 16 to avoid time consuming experimentation and potentially dangerous clinical testing. Accordingly, the system of Claim 16 provides a valuable tool to identify and evaluate potential drugs and drug targets, providing substantial utility and benefit to the public.

Applicants respectfully submit that Claims 13-16 present inventions with substantial utility as exemplified by embodiments described in the specification. As such, the Applicants respectfully submit that Claims 13-16 are allowable. The Examiner is specifically urged to consider the section of the specification entitled "Uses of the Interaction Fingerprint" on pages 8-11.

Rejections Under § 112: Enablement

The Examiner rejected Claims 13-16 under 35 U.S.C. § 112, ¶ 1 for lack of enablement. The Examiner asserted that the specification does not disclose what steps need to be taken to generate an interaction fingerprint. See Office Action, page 5. Specifically, the Examiner asserted that the specification does not provide guidance of how to generate the variables in the interaction fingerprint that characterize protein-ligand interaction. See Office Action, page 5. Furthermore, the Examiner asserted that the specification does not provide enough detail to enable one of skill in the art to compare protein interaction fingerprints. See Office Action, page 6.

The Applicants respectfully submit that the specification provides enough detail to enable one skilled in the art to generate interaction fingerprints and compare them for different proteins. With respect to generating an interaction fingerprint, the specification teaches one to simulate the interaction of a set of ligands with each protein for which an interaction fingerprint is to be created. See specification, page 7, lines 14-19. The set of ligands may consist of a variety of chemical structures. See specification, page 7, lines 9-12. The specification teaches that the

protein-ligand interaction may be characterized by bonding affinity as predicted by the simulated interaction. See specification, page 7, lines 21-23. Those skilled in the art would be aware of several methods to predict bonding affinity between a protein and a ligand. The precise method used to simulate the protein-ligand interactions is not crucial because the instant disclosure is not directed to a method of obtaining binding affinity predictions. Rather, what is disclosed is a method of using interaction predictions, however obtained, to identify protein similarity. Hence, one practicing the instant invention can use any of the methods of predicting binding affinity known in the art. Accordingly, no experimentation, let alone undue experimentation, is required. Rather, those practicing the disclosed method need only choose a known method for simulating protein-ligand interactions. One need not experiment to determine any particular method. It does not follow that because many methods are available, experimentation must be done to determine which methods to use. Any method may be used. For example, the paper cited by the Examiner provides a method for simulating protein-ligand docking suitable for use with the present inventions.

What the instant specification discloses and enables one to practice is to collect the binding affinity data obtained for each ligand into one annotation for a protein called an "interaction fingerprint." The specification describes an example of creating a vector as the interaction fingerprint for a protein. See specification, page 8, lines 5-13. Each variable in the vector corresponds to the simulated interaction between the protein and one of the ligands in a set of ligands. If the method used to simulate the interaction between the protein and the ligand predicts that the ligand will bind to the protein, the corresponding variable is assigned a value of "1." Again, the method of determining whether or not a given ligand binds with the protein is not important. The interaction fingerprint vector will represent a characterization of the chemical response of the protein, which can then be compared with other proteins.

With respect to comparing interaction fingerprints for two different proteins, the specification describes how to perform an "overlap computation" for vectors generated in the above-described example. See specification, page 8, lines 14-23. While not presenting formulas in mathematical form, the specification describes the mathematical steps necessary to perform the overlap computation. First, the specification teaches as one possibility performing a vector multiplication of the two vectors where corresponding entries in the vectors are multiplied and

the results summed to yield a single scalar output value. A specific example is provided with an output value of 4. The specification further teaches that the output value can be normalized by dividing by the square root of the number of "1"s in the first vector multiplied by the number of "1"s in the second vector. In the specific example, a normalized overlap value of 0.8 is obtained. Other methods of comparing the interaction fingerprints would be known to those skilled in the art. For example, the reference cited by the Examiner states that "[t]here are many ways to obtain a similarity index based on a fingerprint of properties." Briem, J. Med. Chem., **1996**, *39*, 3402. The reference goes on to describe specific methods of comparing two vectors. These methods could also be used with the present inventions.

The Examiner also mentioned that the specification provides no direction on how to select a potential target protein. See Office Action, page 5. However, any means known in the art for identifying proteins thought to be operative in a disease may be used to identify a potential target protein. Such means are many and well known in the art. For example, those skilled in the art would know how to identify those proteins involved in a metabolic pathway in a disease pathogen or those human proteins involved in a particular disease. The instant disclosure is not directed to this initial identification. Rather, a method is disclosed that enables one to determine whether the potential target protein should be pursued further (e.g., whether drugs that target that protein will have low side effects). Thus, sufficient description is provided to enable the instant invention.

Rejections Under § 112: Indefiniteness

The Examiner rejected Claims 13-15 under 35 U.S.C. § 112, ¶ 2 as being indefinite. The Examiner asserted that Claim 13 did not contain a step directed to identifying a target protein and that it was unclear what the Applicants intend. See Office Action, p. 7. The applicants have now amended Claim 13 to include a step for identifying the potential target protein as a target protein for pharmaceutical intervention based at least in part on the repeated comparisons. Thus, the Applicants respectfully submit that the Examiner's indefiniteness concerns have been addressed and the Claims are in condition for allowance.

Conclusion

The Applicants respectfully submit that they have addressed all the Examiner's concerns regarding Claims 13-16 in the amendments and remarks above. As such, the Applicants request that Claims 13-16 be allowed.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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